PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Oxytocin during labour and risk of severe postpartum haemorrhage: a population-based cohortnested case-control study
AUTHORS	Jérémie Belghiti, Gilles Kayem, Corinne Dupont, René-Charles Rudigoz, Marie-Hélène Bouvier-Colle and Catherine Deneux-Tharaux

VERSION 1 - REVIEW

REVIEWER	Sohinee Bhattacharya Lecturer, Obstetric Epidemiology University of Aberdeen UK
REVIEW RETURNED	28/10/2011

THE STUDY	The authors have included a STROBE checklist which indicates adequacy of reporting
GENERAL COMMENTS	This manuscript reports a positive association between administration of oxytocin in labour and the risk of postpartum haemorrhage. The study is appropriately designed, measurements appear valid and the statistical analyses are appropriate and robust. I have a few minor comments which, if addressed will make it imminently publishable. 1. Abstract: Suggest changing the opening sentence to "PPH is a major cause of maternal mortality and morbidity worldwide". The conclusion should reflect the fact that oxytocin administration is an independent risk factor for PPH only in cases where postpartum oxytocin administration was not continued. 2. Introduction: Nicely sets the context and importance of this research and specifies the objective. 3. Methods: I am a bit concerned about the fact that the case control study was nested in a randomised control trial whose outcome was PPH. Is it possible that the strict inclusion and exclusion criteria may have introduced selection bias in the present study? Moreover, I am not clear as to whether or not the controls were matched with the cases. If they were not matched, why couldn't the authors have conducted a cohort study with increasing levels of oxytocin administration as exposure? And if they were matched (the age comparison in the 2 groups in Table1 leads me to think so) shouldn't conditional logistic regression have been used? I am also not clear if exposure to oxytocin included both induction and augmentation - if so, these should be analysed separately as the reason for augmentation is usually reduced contractility. 4. Results: The authors mention that 37% of the PPH were due to uterine atony. Given the increased number of operative deliveries in the cases and associated trauma, it would have been good if the authors could have demonstrated an increased odds ratio with atonic PPH per se. 5. The text does not have a conclusion section - it would be good to

	have a definite conclusion as with the abstract.

REVIEWER	Claudio G. Sosa, MD, MsPH, PhD. Associate Professor of Ob-Gyn & Epidemiology School of Medicine / University of Uruguay Competing Interest: I have worked in a similar topic and the authors cited and discussed some articles that I have previously published. I have not any other competing interests.
REVIEW RETURNED	06/11/2011

THE STUDY	I would only like to mention an issue related to the main outcome measure. The authors used the peripartum haemoglobin delta for estimating PPH. The postpartum haemoglobin was the lowest measurement found in the three days after delivery, however, for prepartum haemoglobin, the authors used the one measured during antenatal care, near the end of pregnancy. This period of time may vary too much depending on the characteristics of antenatal care (compliance, etc). In order to have an accurate measure of this surrogate outcome for PPH (and avoid potential misclassification), I would add summary information about the period of time between the measured haemoglobin and the delivery (mean, SD, etc).
GENERAL COMMENTS	From a public health and clinical perspective this study should be regarded as important since the information and its findings may help understand the appropriate use of oxytocin in clinical practice, avoiding the overuse of this obstetric intervention.

VERSION 1 – AUTHOR RESPONSE

Reviewers‘ comments

Reviewer: Sohinee Bhattacharya
Lecturer, Obstetric Epidemiology
University of Aberdeen
UK

The authors have included a STROBE checklist which indicates adequacy of reporting

This manuscript reports a positive association between administration of oxytocin in labour and the risk of postpartum haemorrhage. The study is appropriately designed, measurements appear valid and the statistical analyses are appropriate and robust. I have a few minor comments which, if addressed will make it imminently publishable.

1. Abstract: Suggest changing the opening sentence to "PPH is a major cause of maternal mortality and morbidity worldwide". The conclusion should reflect the fact that oxytocin administration is an independent risk factor for PPH only in cases where postpartum oxytocin administration was not continued.

We changed the opening sentence, as suggested.
We did not change the conclusion because oxytocin administration during labour is also an independent risk factor for PPH in women who receive oxytocin after delivery, although the effect is attenuated in this subgroup and only significant for the highest categories of exposure, as mentioned in the last sentence of the abstract’s results.

2. Introduction: Nicely sets the context and importance of this research and specifies the objective.

We thank the reviewer for this comment

3. Methods: I am a bit concerned about the fact that the case control study was nested in a randomised control trial whose outcome was PPH. Is it possible that the strict inclusion and exclusion criteria may have introduced selection bias in the present study?

It is true that our study population was selected from the Pithagore6 trial. However, this trial was a cluster-randomized and not a person-randomized trial, which means that maternity units were randomised to receive or not the intervention, but not women within the units. No individual consent was needed. All women delivering in the participating units and who had a PPH were included in the cohort. In addition, the 106 participating units covered entire administrative regions. In consequence, the Pithagore6 population constitutes a population-based cohort of all women who delivered in the participating regions and had PPH, during the study period. Because of this design, a selection bias appears very unlikely.

Moreover, I am not clear as to whether or not the controls were matched with the cases. If they were not matched, why couldn't the authors have conducted a cohort study with increasing levels of oxytocin administration as exposure? And if they were matched (the age comparison in the 2 groups in Table1 leads me to think so) shouldn't conditional logistic regression have been used?

As mentioned in the “methods” section page 6, the controls were not matched, but came from a randomly selected representative sample of women who delivered without PPH in the same units during the study period. We have modified the legend of Figure 1 to make this point clearer.
We did not conduct a cohort study because, among all women who delivered in the participating units during the study period, information was collected for all women with PPH but not for all women without PPH but only for a representative sample of those. That is why our study design is a cohort-nested case-control study.

I am also not clear if exposure to oxytocin included both induction and augmentation - if so, these should be analysed separately as the reason for augmentation is usually reduced contractility.
As mentioned in the “study variables” section, induction of labour and oxytocin during labour were two distinct variables. Models estimating the association between oxytocin during labour and PPH were all adjusted for induction of labour, as mentioned in the foot note of table 4.

4. Results: The authors mention that 37% of the PPH were due to uterine atony. Given the increased number of operative deliveries in the cases and associated trauma, it would have been good if the authors could have demonstrated an increased odds ratio with atonic PPH per se.
We agree with this comment and, actually, we believe we have addressed this issue in our study. First, all multivariate analyses were adjusted for operative delivery, so that any confounding effect of this variable has been taken into account in the analysis.
Second, as mentioned in the “analysis” section, “a secondary analysis, using the same control group, limited the case definition to women whose severe PPH was due to uterine atony”; as stated in the results section, this analysis provided similar results. Because of the limit in the number of tables, these results are not detailed in the manuscript. We have added them in an additional table (Table 5) that may be published as supplementary online information if the editors find it useful.

5. The text does not have a conclusion section - it would be good to have a definite conclusion as with the abstract.
We have added a sentence to introduce the conclusion section.

Reviewer: Claudio G. Sosa, MD, MsPH, PhD.
Associate Professor of Ob-Gyn & Epidemiology
School of Medicine / University of Uruguay
Centro Hospitalario Pereira Rossell

This is a very well written study that intents to answer an inconclusive question regarding the oxytocin exposure during labour and the risk of postpartum haemorrhage.
The authors performed a case-control analysis based on data from a cluster randomized controlled trial. From my point of view, the authors have considered the most relevant clinical and epidemiological issues in order to answer the main research question. Clearly, this study has considered some aspects that were not analyzed in previous publications on the same topic. The authors acknowledge the limitations of this paper in terms of general pitfalls of observational studies (such as residual confounding).

I would only like to mention an issue related to the main outcome measure. The authors used the peripartum haemoglobin delta for estimating PPH. The postpartum haemoglobin was the lowest measurement found in the three days after delivery, however, for prepartum haemoglobin, the authors used the one measured during antenatal care, near the end of pregnancy. This period of time may vary too much depending on the characteristics of antenatal care (compliance, etc). In order to have an accurate measure of this surrogate outcome for PPH (and avoid potential misclassification), I would add summary information about the period of time between the measured haemoglobin and the delivery (mean, SD, etc).

We agree with this comment. Although haemoglobin measurement is part of the routine tests during the last trimester of pregnancy in France, it is important to check that the prenatal haemoglobin was not measured too early in pregnancy. Among our study cases, the delay between the prepartum haemoglobin test and the delivery was (mean+/se, 25th, 75th percentile)(days) 11+/-0.7, 0, 14; the great majority (91%)was performed during the month before delivery, indicating an accurate measure of the pre-delivery Hb status and of the actual peripartum drop in Hb as a surrogate for PPH.
This information has been added to the methods section.

>From a public health and clinical perspective this study should be regarded as important since the information and its findings may help understand the appropriate use of oxytocin in clinical practice, avoiding the overuse of this obstetric intervention.

We thank the reviewer for his comments.

VERSION 2 – REVIEW

REVIEWER	Sohinee Bhattacharya Lecturer, Obstetric Epidemiology University of Aberdeen
REVIEW RETURNED	17/11/2011

RESULTS & CONCLUSIONS	Although the article presents a clear message, consideration should be given to the implications for obstetric practice. While I agree that unnecessary oxytocin can be associated with PPH, the take home message from this paper should not be - "STOP using oxytocin". Like all treatments, oxytocin use has side effects - and its use should be based on clinical judgement on a case-by-case basis.